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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/700,338	11/14/2000	Yoshiyuki Ueno	1110-0279P	3959

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EXAMINER
WINKLER, ULRIKE

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 10/02/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/700,338	Applicant(s) UENO, YOSHIYUKI	
	Examiner Ulrike Winkler, Ph.D.	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8 and 10-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8 and 10-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1 and 4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election of Group II in Paper No. 6 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-7 and 9 have been canceled and claims 10-16 have been added. Therefore, claims 8 and 10-16 are currently under consideration.

Information Disclosure Statement

An initialed and dated copy of Applicant's IDS form 1449, Paper Nos. 1 and 4, is attached to the instant Office Action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 8, 10-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kondo et al. (Nature of Medicine, 1997) in view of Harada et al. (Hepatology 1997, see IDS) and further in view of Shirakawa et al. (U.S. Pat. No. 6,114,507).

The instant invention is drawn to a method of preventing **and** treating hepatic cirrhosis (biliary cirrhosis, primary biliary cirrhosis) **or** bile duct disappearance syndrome (caused by an immunological mechanism) (claims 8, 14-16). Bile duct disappearance syndrome is caused by primary biliary cirrhosis (see specification page 13, lines 18-22). The method is achieved by administering a Fas antagonist to a patient. The Fas agonist is a substance that suppresses binding between Fas and Fas ligand (claim 10). The agonist is Fas derivative, a competitive inhibitor comprising ~~is~~ the extracellular domain of Fas. The extracellular domain of Fas may be a truncated form or a chimeric protein between the extracellular domain of Fas and Fc immunoglobulin (claims 11, 12).

Kondo et al. teaches that administration of the soluble form Fas into HbsAg transgenic mice prevented CTL-induced liver disease. Fas ligand (FasL) is expressed in activated T cells and induces apoptosis in Fas-bearing cells. A cytotoxic T lymphocyte (CTL) clone specific for hepatitis B surface antigen (HbsAg) causes an acute liver disease in HBSAg transgenic mice (see figures 3 and 5). The reference teaches the treatment of an animal patient in two experimental hepatitis models with soluble Fas (a Fas derivative) in order to inhibit disease progression in the

patient. The reference does not teach that Fas is expressed on liver cells in primary biliary cirrhosis.

Harada et al. teach that Fas is expressed on a broad range of human tissue, including biliary epithelial cells. The reference teaches that interlobular bile ducts of primary biliary cirrhosis frequently expressed CD95 (Fas) antigen in a cytoplasmic and membranous pattern, in addition a high intensity of CD95 ligand (Fas-ligand) positive mononuclear cells was found in the same pathology samples (see page 1404, column 1, paragraph 2). The findings demonstrate that biliary epithelial cells in primary biliary cirrhosis undergo apoptosis in response to the Fas/Fas ligand mediated cross linking, suggesting that apoptosis is involved in the progression of bile duct injury and loss. The reference does teach using a Fas antagonist to treat ~~the~~ primary biliary cirrhosis.

Shirakawa et al. teach an antibody directed to Fas ligand (see claim 1) and a method of treating systemic or topical pathological conditions caused by the interaction of Fas ligand with Fas. The method comprises administering to a patient a therapeutically effective dose of an anti-Fas ligand antibody, which suppresses Fas ligand induced apoptosis (see claim 22). The reference does not expressly teach treating primary biliary cirrhosis.

The combination of references teaches utilizing a Fas antagonist for the prevention of Fas/Fas ligand interaction *in vivo* in an animal/patient. The references teach that Fas is present in the cells involved in primary biliary cirrhosis. Bile duct disappearance syndrome is caused by primary biliary cirrhosis (see specification page 13, lines 18-22) therefore the same mechanism that are involved in primary biliary cirrhosis would be involved in bile duct disappearance syndrome. It would have been *prima facie* obvious to one of ordinary skill in the art at the time

the invention was made to treat primary biliary cirrhosis by disrupting the Fas/Fas ligand interaction that leads to apoptosis of the cells involved in primary biliary cirrhosis as taught by Harada et al. One having ordinary skill in the art would have a high expectation of success in utilizing Fas antagonists for the purpose of treating bile duct disappearance syndrome and primary biliary cirrhosis in a patient using the antagonist and treatment methods taught by either Kondo et al. and Shirakawa et al. Therefore the instant invention is obvious Kondo et al. in view of Harada et al. and further in view of Shirakawa et al.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for informal communications use 703-308-4426.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ulrike Winkler, Ph.D. 9/26/02